Claims:

1. Use of casein kinase 1, or a nucleic acid molecule encoding the casein kinase 1, for screening for candidate compounds which are capable of (a) inhibiting the activity of casein kinase 1 in phosphorylating a tau protein or (b) binding to casein kinase 1 to inhibit its interaction with a tau protein.

2. The use of claim 1, wherein the casein kinase 1 is a fragment or derivative of full length casein kinase 1 having the amino acid sequence set out between amino acids 1 and 428 inclusive in SEQ ID NO: 1.

3. The use of claim 1 or claim 2, wherein the casein kinase 1 has greater than 80% sequence identity with full length casein kinase 1 having the amino acid sequence set out between amino acids 1 and 428 inclusive of SEQ ID NO: 1.

4. The use of claim 1 or claim 2, wherein the nucleic acid molecule encoding the casein kinase 1 is capable of hybridising under stringent conditions to a nucleic acid molecule encoding full length casein kinase 1 having the amino acid sequence set out in SEQ ID NO: 1.

5. The use of any one of the preceding claims, wherein the tau protein is paired helical filament tau.

6. The use of any one of claims 1 to 4, wherein the tau protein is a fragment or derivative of full length tau protein having the amino acid sequence set out between amino acids 1 and 441 inclusive in SEQ ID NO: 2.

7. The use of any one of the preceding claims, wherein

the tau protein has greater than 80% sequence identity with full tau protein having the amino acid sequence set out between amino acids 1 and 441 inclusive in SEQ ID NO: 2.

8. The use of any one of claims 1 to 5, wherein a nucleic acid molecule encoding the tau protein is capable of hybridising under stringent conditions to a nucleic acid molecule encoding full length tau protein having the amino acid sequence set out in SEQ ID NO: 3.

9. The use of any one of the preceding claims, wherein the casein kinase 1 phosphorylates tau protein at one or more sites selected from the group consisting of (S46/T50), S113, S131, T149, T169, S184, S208, (S210/T212), S214, S237, S238, S241, S258, S262, T263, S285, S289, S305, S341, S352, S356, T361, T373, T386, (S412/S413/T414), S416, S433 and S435 of tau protein.

10. The use of claim 9, wherein the sites of the tau protein are selected from S262 and/or S356.

11. The use of claim 9, wherein the sites of the tau protein at one or more sites selected from the group consisting of S113, S258, S289, S416, S433 and S435.

12. The use of any one of the preceding claims, wherein the screening comprises determining the effect of contacting the candidate compound(s) with a combination of kinases, simultaneously or sequentially applied to the candidate compounds and casein kinase 1.

13. The use of claim 12, wherein the combination of kinases comprises casein kinase 1 (CK1) in combination

with one or more of casein kinase 2 (CK2), protein kinase A (PKA), glycogen synthase kinase 3α (GSK-3α) or glycogen synthase kinase 3β (GSK-3β).

14. The use of claim 12, wherein the combination of kinases comprises casein kinase 1 (CK1) in combination with PKA and GSK-3β.

15. The use of any one of the preceding claims, wherein the screening comprises determining whether, and optionally the extent to which, the candidate compound inhibits the phosphorylation of a substrate by the casein kinase 1.

16. The use of claim 15, wherein the substrate of casein kinase 1 is not a tau protein or a fragment thereof.

17. The use of claim 15 or claim 16, wherein the screening further comprises confirming whether a candidate compound selected in an initial screen has the property of inhibiting the phosphorylation of the tau protein under conditions in which the casein kinase 1 is capable of phosphorylating the site(s) of the tau protein in the absence of the candidate compound.

18. The use of any one of the preceding claims, wherein mass spectroscopy or a site specific recognition agent is used to determine the presence, absence or extent of phosphorylation at one or more sites of the tau protein.

19. The use of claim 18, wherein the site specific recognition agent is a monoclonal antibody.

20. The use of any one of the preceding claims, wherein the screening is carried out in a multiplex assay employing a solid phase on which a plurality of substrates are immobilised.

21. The use of claim 20, wherein the substrates correspond to phosphorylation sites of tau protein.

22. A method of screening for substances which are capable of inhibiting the phosphorylation of a tau protein by casein kinase 1 (CK1), wherein the tau protein comprises one or more phosphorylation sites, the method comprising:

(a) contacting at least one candidate substance, the tau protein and casein kinase 1 under conditions in which the casein kinase 1 is capable of phosphorylating the site(s) of the tau protein in the absence of the candidate substance;

(b) determining whether, and optionally the extent to which, the candidate substance inhibits the phosphorylation of the tau protein at one or more sites of the tau protein by casein kinase 1; and,

(c) selecting the candidate substance which inhibits phosphorylation of the tau protein at one or more of the sites.

23. The method of claim 22, wherein the casein kinase 1 is a fragment or derivative of full length casein kinase 1 having the amino acid sequence set out between amino acids 1 and 428 inclusive in SEQ ID NO: 1.

24. The method of claim 22 or claim 23, wherein the casein kinase 1 has greater than 80% sequence identity with full length casein kinase 1 having the amino acid

sequence set out between amino acids 1 and 428 inclusive of SEQ ID NO: 1.

25. The method of claim 22 or claim 23, wherein the nucleic acid molecule encoding the casein kinase 1 is capable of hybridising under stringent conditions to a nucleic acid molecule encoding full length casein kinase 1 having the amino acid sequence set out in SEQ ID NO: 1.

26. The method of any one of claims 21 to 25, wherein the tau protein is paired helical filament tau.

27. The method of any one of claims 21 to 24, wherein the tau protein is a fragment or derivative of full length tau protein having the amino acid sequence set out between amino acids 1 and 441 inclusive in SEQ ID NO: 3.

28. The method of any one of claims 21 to 27, wherein the tau protein has greater than 80% sequence identity with full tau protein having the amino acid sequence set out between amino acids 1 and 441 inclusive in SEQ ID NO: 3.

29. The method of any one of claims 21 to 28, wherein a nucleic acid molecule encoding the tau protein is capable of hybridising under stringent conditions to a nucleic acid molecule encoding full length tau protein having the amino acid sequence set out in SEQ ID NO: 3.

30. The method of any one of claims 21 to 29, wherein the casein kinase 1 phosphorylates tau protein at one or more sites selected from the group consisting of (S46/T50), S113, S131, T149, T169, S184, S208, (S210/T212), S214, S237, S238, S241, S258, S262, T263,

S285, S289, S305, S341, S352, S356, T361, T373, T386, (S412/S413/T414), S416, S433 and S435 of tau protein.

31. The method of claim 30, wherein the sites of the tau protein are selected from S262 and/or S356.

32. The method of claim 30, wherein the sites of the tau protein at one or more sites selected from the group consisting of S113, S258, S289, S416, S433 and S435.

33. The method of any one of claims 21 to 32, wherein the method comprises determining the effect of contacting the candidate substance(s) with a combination of kinases, simultaneously or sequentially applied to the candidate substances and casein kinase 1.

34. The method of claim 33, wherein the combination of kinases comprises casein kinase 1 (CK1) in combination with one or more of casein kinase 2 (CK2), protein kinase A (PKA), glycogen synthase kinase 3α (GSK-3α) or glycogen synthase kinase 3β (GSK-3β).

35. The method of claim 33, wherein the combination of kinases comprises casein kinase 1 (CK1) in combination with PKA and GSK-3β.

36. The method of any one of claims 21 to 35, wherein the method comprises determining in step (b) whether, and optionally the extent to which, the candidate substance inhibits the phosphorylation of a substrate by the casein kinase 1.

37. The method of claim 36, wherein the substrate of casein kinase 1 is not a tau protein or a fragment

thereof.

38. The method of claim 36 or claim 37, wherein the method further comprises confirming whether a candidate substance selected in an initial screen has the property of inhibiting the phosphorylation of the tau protein under conditions in which the casein kinase 1 is capable of phosphorylating the site(s) of the tau protein in the absence of the candidate substance.

39. The method of any one of claims 21 to 38, wherein the step of determining the presence, absence or extent of phosphorylation at one or more sites of the tau protein employs mass spectroscopy or a site specific recognition agent which is capable of distinguishing between a phosphorylated and a non-phosphorylated site.

40. The method of claim 39, wherein the site specific recognition agent is a monoclonal antibody.

41. The method of any one of claims 21 to 40, wherein the screening is carried out in a multiplex assay employing a solid phase on which a plurality of substrates are immobilised.

42. The method of claim 41, wherein the substrates correspond to phosphorylation sites of tau protein.

43. The method of any one of claims 21 to 42, the method comprising having identified a candidate substance as an inhibitor of casein kinase 1, the further step of optimising the structure of the candidate substance.

44. A method which comprises having identified a

candidate substance by the method of any one of claims 21 to 43, the further step of manufacturing the substance and/or formulating it in pharmaceutical composition.

45. A method of preparing a pharmaceutical composition or medicament, the method comprising:

(i) identifying a casein kinase 1 inhibitor according to any one of claims 1 to 43;

(ii) optimising the structure of the casein kinase 1 inhibitor; and

(iii) preparing the pharmaceutical composition or medicament containing the optimised casein kinase 1 inhibitor.

46. A substance obtainable by the method of any one of claims 1 to 43.

47. Use of a substance of claim 46 for the preparation of a medicament for the treatment of a tauopathy.

48. The use of claim 47, wherein the tauopathy is Alzheimer's disease, frontotemporal dementia with Parkinsonism linked to chromosome 17 (FTDP-17), progressive supranuclear palsy (PSP), Pick's disease, corticobasal degeneration, multisystem atrophy (MSA), neurobasal degeneration with iron accumulation, type 1 (Hallervorden-Spatz), argyrophilic grain dementia, Down's syndrome, diffuse neurofibrillary tangles with calcification, dementia pugilistica, Gerstmann-Sträussler-Scheinker disease, myotonic dystrophy, Niemann-Pick disease type C, progressive subcortical gliosis, prion protein cerebral amyloid angiopathy, tangle only dementia, postencephalitic parkinsonism, subacute sclerosing panencephalitis, Creutzfeldt-Jakob

disease, amyotrophic lateral sclerosis/parkinsonism-dementia complex, non-Guamanian motor neuron disease with neurofibrillary tangles/dementia, and Parkinson's disease.

49. Use of fyn, or a nucleic acid molecule encoding fyn, for screening for candidate compounds which are capable of (a) inhibiting the activity of fyn in phosphorylating a tau protein at a position corresponding to Y394 or (b) binding to fyn to inhibit its interaction with a tau protein at Y394.

48. A method of screening for substances which are capable of inhibiting the phosphorylation of a tau protein at a phosphorylation site at position Y394 by fyn, the method comprising:

(a) contacting at least one candidate substance, the tau protein and fyn under conditions in which the fyn is capable of phosphorylating position Y394 of the tau protein in the absence of the candidate substance;

(b) determining whether, and optionally the extent to which, the candidate substance inhibits the phosphorylation of the tau protein at position Y394 of the tau protein by fyn; and,

(c) selecting the candidate substance which inhibits phosphorylation of the tau protein at position Y394.

49. A method of screening for substances which are capable of inhibiting phosphorylation by a kinase at one or more of the site(s) of a tau protein selected from the group consisting of S68, T69, T71, (T111/S113), S191, S258, S289, (T414/S416), T427, S433, S435 and Y394, the method comprising:

(a) contacting at least one candidate substance, a tau protein which comprises one or more of the phosphorylation sites and a kinase which is capable of phosphorylating the tau protein under conditions in which the kinase is capable of phosphorylating one or more of the sites of the tau protein in the absence of the candidate substance;

(b) determining whether, and optionally the extent to which, the candidate substance inhibits the phosphorylation of the tau protein at one or more sites of the tau protein; and,

(c) selecting the candidate substance which inhibits phosphorylation of the tau protein at one or more of the sites.

50. A method of screening for substances which are capable of promoting dephosphorylation of a tau protein by a phosphatase at one or more of the site(s) of a tau protein selected from the group consisting of S68, T69, T71, (T111/S113), S191, S258, S289, (T414/S416), T427, S433, S435 and Y394, the method comprising:

(a) contacting at least one candidate substance, a tau protein comprising one or more the phosphorylation site and a phosphatase which is capable of dephosphorylating the tau protein under conditions in which the phosphatase is capable of dephosphorylating the site(s) of the tau protein in the absence of the candidate substance;

(b) determining whether, and optionally the extent to which, the candidate substance promotes the dephosphorylation of the tau protein at one or more sites of the tau protein; and,

(c) selecting the candidate substance which promotes dephosphorylation of the tau protein at one or

more of the sites.